III. REMARKS

A. Pending Claims

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are pending. Claims 1, 2, 9, 37, 39, 47, 48, 58, 62, 70, 71, and 76-81 have been amended without prejudice. It is respectfully submitted that no new matter has been added by this amendment.

B. 35 U.S.C. § 112 Rejections

In the Office Action the Examiner rejected claims 2, 9, 21-22, 25-26 and 71 under 35 U.S.C. § 112, second paragraph, "as being indefinite".

In making this rejection, the Examiner specifically referred to the terms "substantially complete release" of claim 2; "a derivative of lovastatin and active metabolite of lovastatin" of claims 9 and 47; and "at the same time nor increasing the bioavailability of lovastatin acid active or total inhibitors" of claim 71. The Examiner also noted that "[c]laim 21, 22, and 25-26 depend on a cancelled claims and thus the scope of these claims are unclear."

In response, claim 2 has been amended without prejudice to remove the term "substantially complete"; claim 9 has been amended without prejudice to remove the term "a derivative of lovastatin, an active metabolite of lovastatin"; claim 47 has been amended without prejudice to remove the term "and its latent and active metabolites"; and claim 71 has been amended without prejudice to remove the term "active or total inhibitors"

In view of the amendments made to claims 2, 9, 47 and 71, the Examiner is respectfully requested to remove the rejections under 35 U.S.C. §112, second paragraph of these claims.

With respect to claims 21, 22, and 25-26, it is respectfully submitted that these claims were amended in the amendment of December 15, 2003 to depend from claim 1. Although claims 21, 22, and 25-26 were listed in the previous response of September 22, 2004 as "original", in the present listing, claims 21, 22, and 25-26 are listed as "previously presented" (as they were previously presented in the amendment of December 15, 2003) and are dependent from claim 1. Therefore, the Examiner is also requested to remove the 35 U.S.C. §112, second paragraph rejection of these claims.

C. 35 U.S.C. § 102 Rejections

1. Cheng et al.

Claims 1-5, 7-13, 18-19, 21-22, 25-26, 28-29, 33-37, 41, 43, 76-77, and 80 were rejected under 35 U.S.C. § 102(b) "as being anticipated by Cheng et al., Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research, 10:1683-1687.

In making the rejection, the Examiner stated that "applicant has not defined 'about 10' in the specification; thus Cheng formulation that yields a T_{max} of 8.7 (with the standard deviation) reads on this limitation. Moreover, it is the examiner's position that if the T_{max} is the same, then the pharmacokinetics will be the same." Further, the Examiner stated that "the intended use recitation, 'administered to humans' does not hold patentable weight in product claims." (emphasis in original).

Although Applicants respectfully disagree with the Examiner's position that a T_{max} of 8.7 described in Cheng et al., which is obtained from the administration of the CRS14 dosage form in Cheng et al. to dogs, would anticipate a mean T_{max} of about 10 obtained in humans (as

explained in our previous responses and in the interviews conducted with the Examiner), the claims have been amended without prejudice to remove the term "about" from the following:

the "about 10" limitation in claims 1, 27, and 39;

the "about 9.8" limitation in claim 76;

the "about 10.6" limitation in claim 77; and

the "about 10.4" limitation in claim 80.

As the "about" term has been removed from these claims with respect to these T_{max} values, it is respectfully submitted that Cheng et al. fail in the very least to teach the T_{max} values as recited in the present claims. Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. § 102(b) of claims 1-5, 7-13, 18-19, 21-22, 25-26, 28-29, 33-37, 41, 43, 76-77, and 80.

2. Alberts et al.

Claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 were rejected under 35 U.S.C. §102(b) "as being anticipated by Alberts et al. (5,376,383)."

In making the rejection, the Examiner stated that "although the prior art does not explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's example 10 provides a release rate over an 18 hour period," and "[t]hus, the T_{max} would inherently fall within [the] instant range." The Examiner further notes that "[t]he recitation of a newly discovered function inherently possessed by the prior art, does not make distinguish it from the prior art," and "it is the applicant's burden to prove otherwise" (citation omitted).

This rejection is traversed. Alberts et al. description that the "Example 10 gave an 85% release over 18 hours" (Column 10, lines 14-15) does not provide any indication or suggestion for correlating a mean time to maximum plasma concentration (Tmax).

It cannot be stated that the formulations of Alberts et al. inherently provide therapeutic T_{max} within the instant range as "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present in the prior art." See *Trintec Industries Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597, 1599 (Fed. Cir. 2002) (citing *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed Cir. 1999)). Further, "[i]nherency is established 'if the natural result flowing from the operation as taught would result in the performance of the questioned function . . . .'" *Scaltech Inc. v. Retec/Tetra LLC*, 60 USPQ2d 1687, 1692 (Fed. Cir. 2001) (citing *Continental Can Co. v. Monsanto Co.*, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)).

It is respectfully submitted that the disclosure of Alberts et al. do not expressly or inherently teach the invention claimed in the present application.

It is respectfully submitted that Alberts et al. fail, in the very least, to teach the T_{max} ranges recited in the present claims. Further, it is respectfully submitted that the T_{max} ranges recited in the present claims are not inherent in the formulations of Alberts et al., as the T_{max} cannot be said to be "necessarily present" in the Alberts et al. disclosure. Therefore, the Examiner is respectfully requested to remove the 35 U.S.C. § 102(b) of claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81.

D. 35 U.S.C. § 103 Rejections

1. Alberts et al. (4,997,658) in view of Chen et al. (5,558,879)\

Claims 1,13, 18, 19, 21, 22, 25-54,57-71 and 76-81 were rejected under 35 U.S.C. § 103(a) "as being unpatentable over Alberts et al. (4,997,658) in view of Chen et al. (5,558,879)." In making the rejection, the Examiner states that with respect to Chen et al., ". . . Figure 6 teaches a T_{max} of the compressed core medicament of approximately 8.5 hours, which reads on *about* 10 hours." (emphasis in original).

This rejection is traversed. Alberts et al. concerns a method of administering an HMG-CoA Reductase Inhibitor utilizing a drug-delivery device for the controlled release of the drug into an environment of use. (See, column 2, lines 55-58). The expression "time-controlled administration" as used in Alberts et al. is deemed to encompass the release of the active form or pro-drug form of the HMG-CoA Reductase Inhibitor into the environment of use over a period of 6 to 24 hrs. The only information in Alberts et al. directed to the in-vivo performance of its formulations is found at Example 2, columns 5-6. In that example, a HMG-CoA Reductase Inhibitor (the ring opened dihydroxy acid of simvastatin) was administered to dogs as either an oral bolus dose or as an oral controlled release preparation. The controlled-release preparation afforded controlled in-vitro release of the drug over a 6-10 hour period. (See, column 6, lines 63-66). Table 2 provides serum cholesterol and plasma drug levels for this example. There is no information contained in this example as to the desired time to maximum plasma concentration after oral administration of the drug (T_{max}). In addition, the peak circulating plasma drug level (which is believed to represent a C_{max}) is very different than the peak level set forth in the present claims.

The Chen et al. '879 patent is directed to controlled-release tablet formulations including a compressed core coated with a first coating for sustained release of the medicament and a second coating for immediate release of a medicament. See e.g., Abstract of Chen et al. The only data provided in this patent directed to in-vivo results is data directed to dosage forms including pseudoephedrine which is not in any way related to, e.g., HMG-CoA Reductase Inhibitors. Therefore, one of ordinary skill in the art would note be motivated to combine the Alberts et al. reference with Chen et al.

With respect to the Examiner's assertion that Figure 6 of Chen teaches a T_{max} of approximately 8.5, it is respectfully submitted that the Examiner's position is not correct. One can not determine a mean T_{max} from a mean plasma concentration/time curve. The mean plasma

concentration/time curve provides the mean concentration at particular time points and does not depict the actual mean T_{max} of the tested patient population.

In any event, claims 1, 27, 39, 48, 58, 62, 70, 71, and 76-81 have been amended without prejudice to remove the "about" language from the lower limit of the T_{max} range recited in the claims. Therefore, even if the Tmax is 8.5 hours for Chen, it does not teach or suggest a Tmax of 10 to about 32 hours as presently claimed.

In view of the above, it is respectfully submitted that the combination of Alberts et al. with Chen et al. fail to teach, hint or suggest the T_{max} ranges recited in the present claims. Therefore, the Examiner is respectfully requested to remove this rejection.

2. Chen et al. (5,837,379)

Claims 1, 13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 were rejected under 35 U.S.C. § 103(a) "as being unpatentable over US patent 5,837,379 to Chen et al."

This rejection is traversed. The Chen et al. '379 patent is directed to controlled release dosage forms which comprise a medicament which may be lovastatin, fluvastatin, simvastatin, or pravastatin. (See, e.g., Column 2, lines 64-65 of Chen). The only data provided in this patent directed to in-vivo results is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., HMG-CoA Reductase Inhibitors. None of the exemplified formulations includes a drug that is a HMG-CoA Reductase Inhibitor, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone a HMG-CoA Reductase Inhibitor. Further, there is no statement in Chen et al. relating to Tmax, and there is no suggestion in Chen et al. that the in vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxyl substituted napthalenes.

It is respectfully submitted that Chen et al. fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. Therefore, the Examiner is requested to remove this rejection.

3. Cheng et al.

Claims 48-50, 58-59, 62-63, 65-66, 68-70, 71, 78-79, and 81 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Cheng et al, Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (19923), 10:1683-1687."

This rejection is traversed. The Cheng reference describes studies conducted with seven sustained/controlled-release dosage forms of lovastatin or simvastatin. The in-vivo performance of these formulations was evaluated in dogs and healthy volunteers. The results are reported Table II on page 1685 and Table V page 1687 of the Cheng reference.

In Table V, the controlled-release formulations are reported to have a T_{max} 4.2±0.7 hours (MODS8) and 4.7±1.0 hours (MODS14, representing the T_{max} for an 8 hour formulation and a 14 hour formulation, respectively. It is apparent from this data that these formulations have been designed to provide a relatively rapid rise in plasma concentration to T_{max}, and it is respectfully submitted that the results are not suggestive of a mean T_{max} as set forth in the present claims (which occurs at a time which is more than double the time for the T_{max} of the 14 hour Cheng formulation). It is noted that the T_{max} reported in Table V is the T_{max} for total HMG-CoA Reductase Inhibitors in healthy subjects receiving a single dose of 20 mg simvastatin.

Turning now to Table II of the Cheng reference, this table provides pharmacokinetic parameters of total HMG-CoA Reductase Inhibitors in dogs receiving a single oral dose of 80 mg lovastatin. The T_{max} reported therein for the sustained and controlled-release formulations are as follows: SRT8 had a T_{max} of 1.8±0.4; SRT14 had a T_{max} of 2.3±0.8; CRS8 had a T_{max} of

4.0±0.0; and CRS14 had a T_{max} of 7.5±1.2. However, as previously noted to the Examiner, it is respectfully submitted that the data concerning dog values is not instructive with respect to the performance of these formulations in humans given that the Cheng reference at page 1687, left column, penultimate paragraph states the following: "By comparing the AUC and C_{max} ratios for CRS and MODS formulations in dogs (Tables II and III) to those in humans (Table V), it can be concluded that the dog may not be a good model for predicting relative bioavailability of lovastatin or simvastatin in these formulations in humans)." (Emphasis added). Therefore, it is respectfully submitted that one of ordinary skill in the art would not conclude that the pharmokinetics in dog would yield similar functional results in humans.

In view of the pharmacokinetic data in Cheng et al. with respect to the administration of the lovastatin formulations described therein to dogs and the simvastatin formulations described therein to humans, it is respectfully submitted that Cheng et al. fails to teach, hint or suggest the T_{max} ranges as recited in the present claims. Therefore, the Examiner is requested to remove this rejection.

4. Klimstra et al. (5,668,134)

Claims 1-13, 18, 19, 21, 22, 25-48, 70-71, 76-77, and 80 were rejected under 35 U.S.C. § 103(a) "as being unpatentable over Klimstra et al (5,668,134)." In making the rejection, the Examiner stated that ". . . Klimstra teaches a variety of medicaments that would benefit from the use of a once-a-day dosage form that provides a peak serum levels after daylight hours, i.e., a T_{max} of 16 hours or so." The Examiner cites Table 16 of Klimstra et al. as teaching "lomefloxacin plasma concentrations wherein the T_{max} is 16 hours."

This rejection is traversed. The study of Example 1 which utilizes a Maxaquin® (lomefloxacin HCl) oral dosage form indicates that the mean pharmacokinetic parameter value obtained for T_{max} = 1.5 h. (See, e.g., col. 26, line 23). Although the Examiner relies on Table 16 of Klimstra et al. as describing "lomefloxacin plasma concentrations wherein the T_{max} is 16

hours", it is respectfully pointed out that the administration of the dose was at the 14th hour of the scheduled time interval. Therefore, the T_{max} measured at the 16th hour is consistent with a dosage form which provides an actual T_{max} of about 1.5 hours as indicated in Example 1. In support of this, the Examiners attention is directed to the footer after Table 6, in column 49, wherein it states that "**Hour 16 = Day 5 2-hours following last active dose.**" Therefore, as the dosage form was administered 2 hours prior to Hour 16, the T_{max} alleged by the Examiner to be 16 hours is would actual be 2 hours as this was the time to maximum plasma concentration after oral administration of the lomefloxacin dosage form.

In view of the above, it is respectfully submitted that Klimstra et al. fail in the very least to teach, hint or suggest the T_{max} values recited in the present claims. Therefore, the Examiner is respectfully requested to remove this rejection.

5. Klimstra et al (5,668,134) in view of Alberts et al. (4,997,658)

Claims 48-54, 57-69, 78-79 and 81 were rejected under 35 U.S.C. §103(a) "as being unpatentable over Klimstra et al (5,668,134) in view of Alberts et al (4,997,658)."

This rejection is traversed. It is respectfully submitted that Klimstra et al. fails to teach, hint or suggest an oral dosage form which provides the T_{max} ranges recited in the present claims for the same reasons as presented above. It is respectfully submitted that Alberts et al. fails to cure the deficiencies of Klimstra as neither reference alone or in combination teach, hint or suggest the T_{max} ranges recited in the present claims.

Therefore, the Examiner is respectfully requested to remove this rejection.

E. Double Patenting

Claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 were rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 1-12 of U.S. Patent No. 5,916,595 and 6,485,748."

Claims 1-13, 18, 19, 21, 22, 25-54, 57-71 and 76-81 were also provisionally rejected under the judicially created doctrine of obvious-type double patenting "as being unpatentable over claims 1-13, 18-19, 21-22, 25-29, 31-47, 76-77, and 80 of copending Application No. 09/435,576."

The double patenting rejection over U.S. Patent No. 6,485,748, is traversed. It is respectfully submitted that the claims of U.S. Patent No. 6,485,748 fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. Therefore, the Examiner is respectfully requested to remove this rejection.

With respect to the double-patenting rejection of the claims over the claims of U.S. Patent No. 5,916,595, and the provisional double-patenting rejection of the claims over copending Application No. 09/435,576, Applicants will consider the filing of a terminal disclaimer with respect to this patent and application upon notice from the Examiner that the claims are otherwise allowable.

IV. Conclusion

It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance. According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____

Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940